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(74) Agents: VINCENT, Matthew, P. et al.; Foley, Hoag & Eliot LLP, One Post Office Square, Boston, MA 02109 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

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(54) Title: NEUROPROTECTIVE METHODS AND REAGENTS

(57) Abstract

One aspect of the present application relates to a method for limiting damage to neuronal cells by ischemic or epoxic conditions, e.g., such as may be manifest by a reduction in brain infarct volume, by administering to an individual a hedgehog therapeutic or ptc therapeutic in an amount effective for reducing cerabral infarct volume.

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We claim:

1. A method for limiting damage to neuronal cells by ischemic or epoxic conditions, comprising administering to an individual a *ptc* therapeutic in an amount effective for reducing cerebral infarct volume relative to the absence of administeration of the *ptc* therapeutic.

2. A method for protecting cerebral tissue of a mammal against the repercussions of ischemia which comprises administering to the mammal in need thereof a therapeutically effective amount of the *ptc* therapeutic.

3. A method for the treatment of cerebral infarctions which comprises administering to a patient in need thereof a therapeutically effective amount of the *ptc* therapeutic.

4. A method for the treatment of cerebral ischemia which comprises administering to a patient in need thereof a therapeutically effective amount of the *ptc* therapeutic.

5. A method for the treatment of stroke which comprises administering to a patient in need thereof a therapeutically effective amount of the *ptc* therapeutic.

6. A method for the treatment of transient ischemia attack which comprises administering to a patient in need thereof a therapeutically effective amount of the *ptc* therapeutic.

7. The method of any of claims 1-6, wherein the *ptc* therapeutic binds to *patched* and mimics *hedgehog*-mediated *patched* signal transduction.

8. The method of claim 7, wherein the *ptc* therapeutic is a small organic molecule.

9. The method of claim 7, wherein the binding of the ptc therapeutic to *patched* results in upregulation of patched and/or gli expression.

10. The method of any of claims 1-6, wherein the *ptc* therapeutic is a small organic molecule which interacts with neuronal cells to mimic *hedgehog*-mediated *patched* signal transduction.

11. The method of any of claims 1-6, wherein the *ptc* therapeutic mimics *hedgehog*-mediated *patched* signal transduction by altering the localization, protein-protein binding and/or enzymatic activity of an intracellular protein involved in a *patched* signal pathway.

12. The method of any of claims 1-6, wherein the *ptc* therapeutic alters the level of expression of a *hedgehog* protein, a patched protein or a protein involved in the intracellular signal transduction pathway of *patched.*

13. The method of claim 12, wherein the *ptc* therapeutic is an antisense construct which inhibits the expression of a protein which is involved in the signal transduction pathway of *patched* and the expression of which antagonizes *hedgehog*-mediated signals.

14. The method of claim 13, wherein the antisense construct is an oligonucleotide of about 20-30 nucleotides in length and having a GC content of at least 50 percent.

15. The method of claim 14, wherein the antisense oligonucleotide is selected from the group consisting of: 5'-GTCCTGGCGCCGCCGCCGCCGTCGCC;

5'-TTCCGATGACCGGCCTTTCGCGGTGA; and

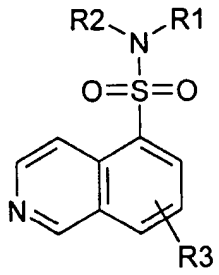
5'-GTGCACGGAAAGGTGCAGGCCACACT

16. The method of claims 12, wherein the *ptc* therapeutic is a small organic molecule which binds to *patched* and regulates *patched*-dependent gene expression.

17. The method of claim 11, wherein the *ptc* therapeutic is an inhibitor of protein kinase A.

18. The method of claim 17, wherein the PKA inhibitor is a 5-isoquinolinesulfonamide

19. The method of claim 18, wherein the PKA inhibitor is represented in the general formula:



wherein,

R_1 and R_2 each can independently represent hydrogen, and as valence and stability permit a lower alkyl, a lower alkenyl, a lower alkynyl, a carbonyl (such as a carboxyl, an ester, a formate, or a ketone), a thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), an amino, an acylamino, an amido, a cyano, a nitro, an azido, a sulfate, a sulfonate, a sulfonamido, $-(CH_2)_m-R_8$, $-(CH_2)_m-OH$, $-(CH_2)_m-O$-lower alkyl, $-(CH_2)_m-O$-lower alkenyl, $-(CH_2)_n-O-(CH_2)_m-R_8$, $-(CH_2)_m-SH$, $-(CH_2)_m-S$-lower alkyl, $-(CH_2)_m-S$-lower alkenyl, $-(CH_2)_n-S-(CH_2)_m-R_8$, or

R_1 and R_2 taken together with N form a heterocycle (substituted or unsubstituted);

R_3 is absent or represents one or more substitutions to the isoquinoline ring such as a lower alkyl, a lower alkenyl, a lower alkynyl, a carbonyl (such as a carboxyl, an ester, a formate, or a ketone), a thiocarbonyl (such as a thioester, a thioacetate, or a thioformate), an amino, an acylamino, an amido, a cyano, a nitro, an azido, a sulfate, a sulfonate, a sulfonamido, $-(CH_2)_m-$

R_8, $-(CH_2)_m$-OH, $-(CH_2)_m$-O-lower alkyl, $-(CH_2)_m$-O-lower alkenyl, $-(CH_2)_n$-O-$(CH_2)_m$-R_8, $-(CH_2)_m$-SH, $-(CH_2)_m$-S-lower alkyl, $-(CH_2)_m$-S-lower alkenyl, $-(CH_2)_n$-S-$(CH_2)_m$-R_8;

R_8 represents a substituted or unsubstituted aryl, aralkyl, cycloalkyl, cycloalkenyl, or heterocycle; and

n and m are independently for each occurrence zero or an integer in the range of 1 to 6.

20. The method of claim 17, wherein the PKA inhibitor is cyclic AMP analog.

21. The method of claim 17, wherein the PKA inhibitor is selected from the group consisting of N-[2-((p-bromocinnamyl)amino)ethyl]-5-isoquinolinesulfonamide, 1-(5-isoquinoline-sulfonyl)-2-methylpiperazine, KT5720, 8-bromo-cAMP, dibutyryl-cAMP and PKA Heat Stable Inhibitor isoform α.

22. The method of claim 5, wherein the stroke is a thrombotic stroke.

23. The method of claim 5, wherein the stroke is an embolic stroke

24. The method of claim 1, wherein the hypoxic conditions result in cerebral hypoxia.

25. The method of claim 1, wherein the conditions result in progressive loss of neurons due to oxygen deprivation

26. The method of any of claims 1-6, wherein patient is being treated prophylactically.

27. The method of claim 1, wherein the patient is hypotensive.

28. The method of claim 1, wherein the conditions result in progressive loss of neurons due to oxygen deprivation

29. The method of any of claims 1-6, wherein the *ptc* therapeutic is administered as part of a therapy including administering one or more of an anticoagulation, an antiplatelet agent, a thrombin inhibitors, and/or a thrombolytic agent.

30. The method of any of claims 1-6, wherein the *ptc* therapeutic is administered as part of a therapy including vascular surgery.

31. The method of claim 30, wherein the vascular surgery comprises carotid endarterectomy.

32. The method of any of claims 1-6, wherein treatment of the patient with the *ptc* therapeutic results in atleast a 25% reduction in cerebral infarct volumes relative to absence of treatment with the *ptc* therapeutic.

33. The method of claim 32, wherein treatment of the patient with the *ptc* therapeutic results in atleast a 50% reduction in cerebral infarct volumes relative to absence of treatment with the *ptc* therapeutic.

34. The method of claim 32, wherein treatment of the patient with the *ptc* therapeutic results in atleast a 70% reduction in cerebral infarct volumes relative to absence of treatment with the *ptc* therapeutic.

35. A therapeutic preparation of a small molecule antagonist of *patched*, which *patched* antagonist is provided in a pharmaceutically acceptable carrier and in an amount sufficient to provide protection against neuronal cell death under ischemic and/or hypoxic conditions.

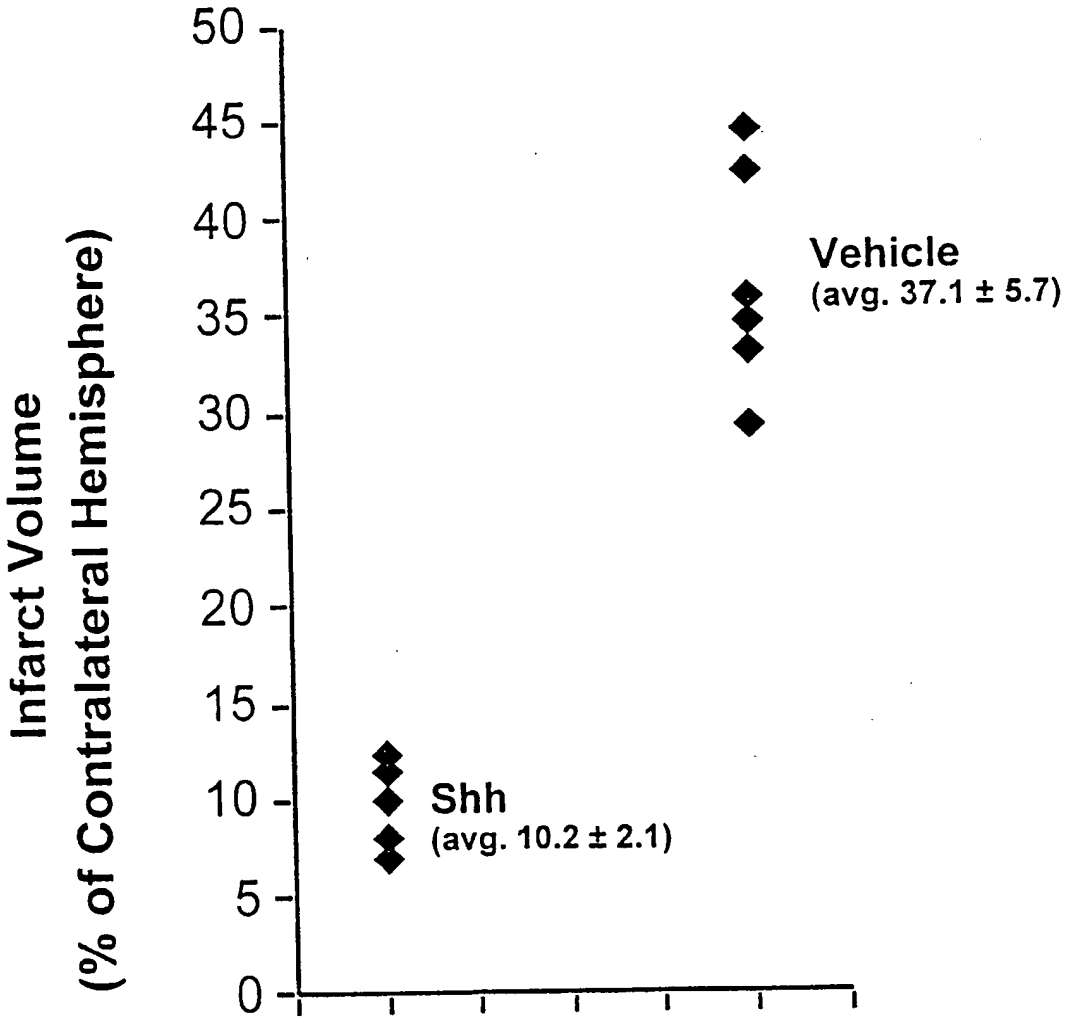
36. The preparation of claim 35, which *patched* antagonist binds to *patched*.

37. The preparation of claim 35, wherein the *patched* antagonist is provided in an amount sufficient to produce, upon a dosage regimen of 7 days, at least a 70% decrease in infarct volume in an MCAO model relative to the absence of the *patched* antagonist.

38. The preparation of claim 37, wherein the *patched* antagonist is provided in an amount sufficient to produce, upon a dosage regimen of 3 days, at least a 70% decrease in infarct volume in an MCAO model relative to the absence of the *patched* antagonist.

39. A method for limiting damage to neuronal cells by ischemic or epoxic conditions, comprising administering to a patient a gene activation construct which recombines with a genomic *hedgehog* gene of the patient to provide a heterologous transcriptional regulatory sequence operatively linked to a coding sequence of the *hedgehog* gene.

Figure 1


Infarct Volume
(% of Contralateral Hemisphere)
50
45
40
35
30
25
20
15
10
5
0
Vehicle
(avg. 37.1 ± 5.7)
Shh
(avg. 10.2 ± 2.1)

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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A3

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(88) Date of publication of the international search report:
1 April 1999 (01.04.99)

(54) Title: NEUROPROTECTIVE METHODS AND REAGENTS

(57) Abstract

One aspect of the present application relates to a method for limiting damage to neuronal cells by ischemic or epoxic conditions, e.g., such as may be manifest by a reduction in brain infarct volume, by administering to an individual a hedgehog therapeutic or ptc therapeutic in an amount effective for reducing cerabral infarct volume.

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INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/US 98/13387

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/47

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 519 035 A (MAIESE KENNETH ET AL) 21 May 1996 see abstract see column 2, line 20-34; claims 1-5; examples 1,2 ---	1-12, 16-19, 21-28, 30-38
X	SATOH ET AL.: "Neuroprotective properties of a protein kinase inhibitor against Ischemia-induced neuronal damage in rats and gerbils" BRITISH JOURNAL OF PHARMACOLOGY, vol. 118, no. 7, 1996, pages 1592-1596, XP002092077 see abstract --- -/--	1-12, 16-19, 22-28, 30-38

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

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Date of the actual completion of the international search	Date of mailing of the international search report
3 February 1999	18/02/1999

Name and mailing address of the ISA	Authorized officer
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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter ɔnal Application No
PCT/US 98/13387

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category '	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	MAIESE ET AL.: "Protein Kinases Modulate the Sensitivity of Hippocampal Neurons to Nitric Oxide Toxicity and Anoxia" JOURNAL OF NEUROSCIENCE RESEARCH, vol. 36, no. 1, 1993, pages 77-87, XP002092078 see abstract see page 79, column 1, paragraph 1 - page 81, column 2, paragraph 2; figure 1 see page 83, column 2, paragraph 2 - page 84, column 1, paragraph 3 ---	1-12, 16-28, 30-38
X	PHILLIS ET AL.: "Mechanism of glutamate and aspartate release in the ischemic rat cerebral cortex" BRAIN RESEARCH, vol. 730, no. 1-2, 1996, pages 150-164, XP002092079 see abstract; figure 7; tables 2,3 ---	1-12, 16-28, 30-38
X	EP 0 187 371 A (ASAHI CHEMICAL IND ;HIDAKA HIROYOSHI (JP)) 16 July 1986 see abstract see page 2, line 1-10; example 4 see page 8, line 6 - page 14, line 4 ---	1-12, 16-19, 22-28, 30-38
P,X	WO 98 12326 A (CHUANG PAO TIEN ;HARVARD COLLEGE (US); MCMAHON ANDREW P (US)) 26 March 1998 see page 3, line 15 - page 9, line 10; claim 13 -----	1-14,40

1

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

I. .national application No.

PCT/US 98/ 13387

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 1-34, 40
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 1-34, 40 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: -
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
See FURTHER INFORMATION SHEET PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

In view of the large number of compounds, which are defined by the general definition(s)/formulae used in claims 1-20, 22-40, the search had to be restricted for economic reasons. The search was limited to the compounds for which pharmacological data was given and/or the compounds mentioned in the claims, and to the general idea underlying the application.
(See Guidelines, chapter III, paragraph 2.3).

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter onal Application No
PCT/US 98/13387

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5519035 A	21-05-1996	NONE	
EP 0187371 A	16-07-1986	JP 1795364 C	28-10-1993
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